Chiral Auxiliary-Directed Asymmetric Nucleophile Additions to Arene–Manganese Tricarbonyl Complexes

Anthony J. Pearson* and Ping Y. Zhu

Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106

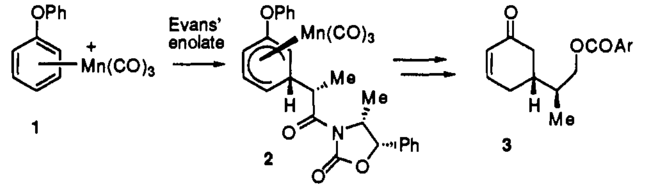
Wiley J. Youngs,† John D. Bradshaw, and
David B. McConville

Department of Chemistry
The University of Akron
Akron, Ohio 44325

Received May 24, 1993

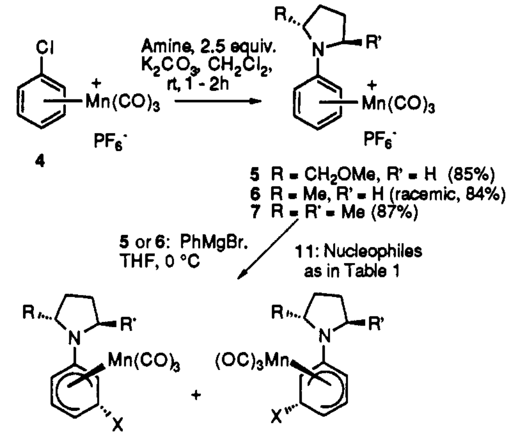
Arene–manganese tricarbonyl complexes are reactive toward a variety of carbon nucleophiles, giving rise to neutral cyclohexadienyl–$Mn(CO)_3$ complexes.[1] An alkoxy substituent on the aromatic ring directs nucleophile addition to the meta position, and this leads to methodology for the conversion of anisole derivatives to substituted cyclohexenones.[1] Recently, a study of chiral nonracemic enolate nucleophile addition to complex **1** was reported to give modest asymmetric induction (*ca.* 55% e.e., Scheme I),[2] similar to earlier reports from our laboratory of chiral nucleophile additions to dienyliron[3] and dienemolybdenum[4] complexes, but there are no other reports of asymmetric nucleophile additions.

Scheme I



+ Diastereomer (3.5:1)

Scheme II



5 R = CH_2OMe, R' = H (85%)
6 R = Me, R' = H (racemic, 84%)
7 R = R' = Me (87%)

8 R = CH_2OMe, R' = H, X = Ph
10 R = Me, R' = H (rac), X = Ph
12 R = R' = Me, X = a, b, or c

9 R = CH_2OMe, R' = H, X = Ph
11 R = Me, R' = H (rac), X = Ph
13 R = R' = Me, X = a, b, or c

(a) X = H; (b) X = Me; (c) X = Ph

We are currently studying nucleophile additions to arene–metal complexes that have amino substituents as recoverable chiral auxiliaries. Our investigation began with the manganese complexes **5** ($[\alpha]^{22}_D = -131.7°$ ($c = 1.16$, CH_2Cl_2) and **6**, which were readily prepared by reaction of chlorobenzene–$Mn(CO)_3$ hexafluorophosphate[5] (**4**) with optically pure *O*-methylprolinol and racemic 2-methylpyrrolidine, respectively (Scheme II). The reactions of complexes **5** and **6** with PhMgBr in THF at 0 °C are summarized in Scheme II. Diastereomeric excesses of 44% and *ca.* 40%, respectively, for these reactions were measured by integration of ^1H NMR spectra of the crude product mixtures; the structures of the major stereoisomers were assigned by analogy with later results using complex **7**. While the results indicate the feasibility of 1,5-asymmetric induction during these reactions, the selectivities are too low to be of value in organic synthesis. We had originally anticipated that **5** and **6** would show a preference for conformation **A** (Figure 1), in which the substituent (R) is placed *anti* to the $Mn(CO)_3$ group. ^1H NMR spectroscopy of the carefully purified complex (to remove paramagnetic impurities) at ambient temperature, however, showed the presence of *both* conformers **A** and **B** (**5**, *Me*O, two sharp singlets in a ratio of 1:1.2 at δ 3.25 and 3.36 ppm). At 70 °C, only one methoxy resonance was observed (δ 3.33), indicating rapid conformational interconversion, but the experiment was complicated by the *in situ* decomplexation of **5** by reaction with the solvent (CD_3CN).[6] On cooling of the NMR sample back to ambient temperature, the two methoxy signals reappeared in the same ratio (together with the aromatic product from demetalation at δ 3.31). Owing to the problem of accompanying decomplexation, we have not attempted to determine any thermodynamic parameters for this interconversion.

Nucleophiles are known to add *anti* to the $Mn(CO)_3$ group,[1] and addition of PhMgBr to conformation **B** proceeds with *zero* diastereoselectivity, there being no steric hindrance from the R substituent along either trajectory for meta addition.[7] Addition to conformation **A** must occur with *ca.* 9:1 selectivity at the meta position remote from the R group, accounting for the observed overall diastereoselectivity of *ca.* 2.5:1. A high level of stereocontrol should therefore be attainable by using a complex of structure **7**, where both conformations present an identical spatial arrangement to an incoming nucleophile. This complex ($[\alpha]^{22}_D = -180.4°$ ($c = 1.03$, CH_2Cl_2)) was readily prepared by reaction of **4** with (*R*,*R*)-2,5-dimethylpyrrolidine.[8] Reactions of nucleophiles with **7** under a variety of reaction conditions are summarized in Table I. Modest selectivity was observed with $LiAlH_4$, and this was improved by using the bulkier hydride source, lithium tri-*sec*-butylborohydride (L-Selectride, Aldrich). Choice of

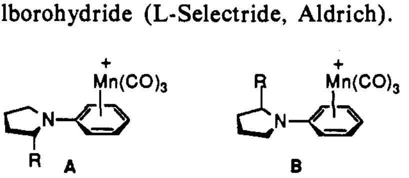


Figure 1. Conformations of Complexes **5** and **6**.

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† Author to whom correspondence concerning X-ray structures should be addressed.

(1) For a recent review, see: Pike, R. D.; Sweigart, D. A. *Synlett* **1990**, 565.

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(3) Pearson, A. J.; Blystone, S. L.; Nar, H.; Pinkerton, A. A.; Roden, B. A.; Yoon, J. *J. Am. Chem. Soc.* **1989**, *111*, 134. Pearson, A. J.; Yoon, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1467.

(4) Pearson, A. J.; Blystone, S. L.; Roden, B. A. *Tetrahedron Lett.* **1987**, *28*, 2459. Pearson, A. J.; Khetani, V. D.; Roden, B. A. *J. Org. Chem.* **1989**, *54*, 5141.

(5) Pauson, P. L.; Segal, J. A. *J. Chem. Soc., Dalton Trans.* **1975**, 1677.

(6) Reaction of arene–$Mn(CO)_3$ cations with warm acetonitrile is known to lead to decomplexation, see ref 5.

(7) Semmelhack *et al.* have discussed the effect of bulky substituents on the conformation of arene–$Cr(CO)_3$ complexes and their influence on regioselectivity during nucleophile addition: Semmelhack, M. F.; Garcia, J. L.; Cortes, D.; Farina, R.; Hong, R.; Carpenter, B. K. *Organometallics* **1983**, *2*, 467. While we have not ruled out the possibility of the chiral auxiliary influencing the orientation of the $Mn(CO)_3$ group in conformation B, thereby leading to non-zero diastereoselectivity, the X-ray structure of the related complex **7** shows that the $Mn(CO)_3$ group is almost symmetrical with respect to the two meta positions (dihedral angle N–C(4)–Mn–C(3) = 6.6°). It seems unlikely that the correlation of selectivity with conformation discussed in the text is coincidental. PCModel calculations on complexes **6** and **7** are in very close agreement with this value, giving a dihedral angle of *ca.* 5.1°.

(8) Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083. Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755.

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Table I. Reactions of Nucleophiles with Complex **7** To Give Complexes **12** and **13**

entry	nucleophile	reaction conditions	product (yield, %)	d.e. (%)[a]
1	$LiAlH_4$	THF, rt,[b] 5 min	**a**(25)	33
2	L-Selectride	THF, rt, 10 min	**a**(75)	54
3	L-Selectride	THF, 0 °C, 17 min	**a**(64)	59
4	L-Selectride	THF, –78 °C, 10 min	**a**(55)	67
5	L-Selectride	THF, –95 °C, 30 min	**a**(61)	71
6	L-Selectride	CH_2Cl_2, –78 °C, 15 min	**a**(67)	75
7	L-Selectride	CH_2Cl_2, –90 °C, 15 min	**a**(45)	77
8	MeLi	CH_2Cl_2, –90 °C, 30 min	**b**(57)	50
9	PhLi	THF, –78 °C, 10 min	**c**(52)	35
10	PhLi	CH_2Cl_2, –45 °C, 35 min	**c**(33)	73
11	PhLi	CH_2Cl_2, –78 °C, 20 min	**c**(57)	77
12	PhLi	CH_2Cl_2, –90 °C, 10 min	**c**(47)	81
13	PhMgBr	THF, 0 °C, 10 min	**c**(72)	83
14	PhMgBr	THF, –78 °C, 21 h	**c**(60)	90
15	PhMgBr	CH_2Cl_2, 0 °C, 30 min	**c**(low)[c]	87

[a] Measured by integration of ^{1}NMR spectrum of crude product mixture prior to chromatographic purification. [b] Room temperature. [c] Several unidentified side products were observed.

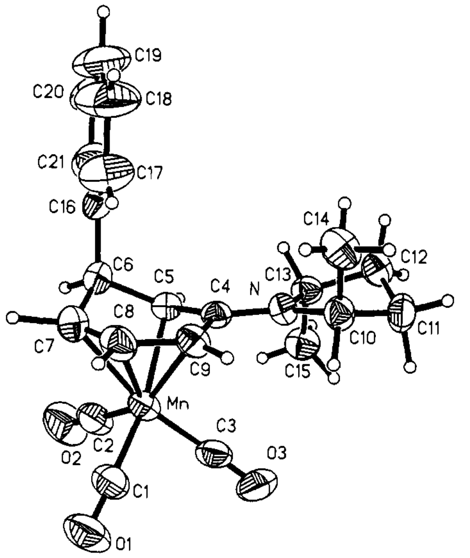

Figure 2. X-ray structure of complex **12c**. Numbering of atoms is arbitrary. See ref 9 for description. Selected bond lengths (Å): Mn–C(1), 1.803(3); O(1)–C(1), 1.150(4); Mn–C(4), 2.292(3); Mn–C(8), 2.118(3); C(4)–C(5), 1.416(5); C(6)–C(7), 1.511(5); N–C(4), 1.364(4); N–C(10), 1.476(4); C(11)–C(12), 1.517(5); C(6)–C(16), 1.515(4); C(16)–C(17), 1.363(7).

solvent and/or reaction temperature is important, best results being obtained in CH_2Cl_2 at *ca.* -90 °C (entry 7). Reaction of **7** with methyllithium (CH_2Cl_2, -90 °C) gave a 75:25 mixture of diastereomers **12b** and **13b**, which could not be further improved. Phenyllithium addition was sensitive to temperature and solvent (entries 9–12) and gave a diastereomeric excess of 81% (9:1 ratio) under optimum conditions. Reaction with PhMgBr was found to be cleaner, since PhLi also attacks at CO ligand leading to demetalation, but the Grignard reagent gave the best selectivity in THF at low temperature (entry 14). It is noteworthy that PhMgBr addition to **7** gave *ca.* 11:1 selectivity under conditions identical to those used with complexes **5** and **6**.

The stereochemical outcome of these reactions was rigorously established by single-crystal X-ray structure determination on **12c**, recrystallized from ethanol/pentane ($[\alpha]^{25}D = -187.0°$ ($c = 0.88$, CH_2Cl_2)), which clearly shows that nucleophile addition occurs preferentially at the meta position that is remote from the pyrrolidine methyl substituent (Figure 2),[9] thereby providing an unusual example of 1,5-stereocontrol. That the methyl groups on complex **7** are indeed axial was confirmed also by X-ray crystallography (Figure 3).[9] Cationic arene–metal complexes are usually obtained as amorphous powders and have not previously been rigorously characterized by X-ray techniques,[10] but careful crystallization of **7** from methanol/CH_2Cl_2 gave excellent single crystals. The structure indicates that the preferred trajectory for nucleophile addition is at the remote meta position (C6 in Figures 2 and 3), but the relatively long distance between reaction site and chiral center leads to poor selectivity with sterically undemanding nucleophiles (e.g., $LiAlH_4$ vs L-Selectride). Future work will be directed at using this analysis to design more useful chiral auxiliaries as well as studying the synthetic applications of this chemistry.

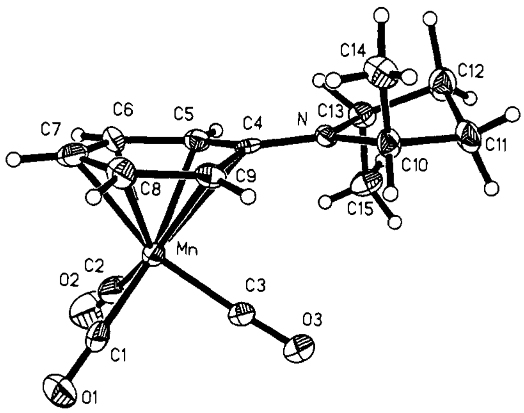

Figure 3. X-ray structure of complex **7**. Numbering of atoms is arbitrary. See ref 9 for description. Selected bond lengths (Å): Mn–C(1), 1.810(5); O(1)–C(1), 1.144(6); Mn–C(4), 2.420(4); Mn–C(6), 2.162(5); Mn–C(8), 2.151(5); C(4)–C(5), 1.434(6); C(6)–C(7), 1.396(7); N–C(4), 1.325(5); N–C(10), 1.495(6); C(11)–C(12), 1.532(7).

Acknowledgment. We are grateful to the U.S. Public Health Service, National Institutes of Health (GM 36925 to A.J.P.) and NASA/Lewis Research Center (NCC 3-225 to W.J.Y.) for financial support.

Supplementary Material Available: Full details of the X-ray structures of complexes **7** and **12c**, including tables of atomic coordinates, bond lengths, bond angles, and anisotropic displacement coefficients (21 pages); observed and calculated structure factors (13 pages). Ordering information is given on any current masthead page.

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(9) Since the dimethylpyrrolidine is of known absolute stereochemistry, the X-ray structure of **12c** also establishes the absolute configuration at the stereocenter arising from nucleophile addition. Typical bond lengths were observed for both complexes. In complex **7**, the Mn is bound to all six carbons of the phenyl ring. The Mn is shifted away from the amine substituent as shown by the longer Mn-to-C4 vs -C7 distances (2.420(4), 2.157(5) Å, respectively) but is centered laterally as shown by the distances from Mn to C6 and C8 (2.162(5), 2.151(5) Å, respectively) and to C5 and C9 (2.218(5), 2.203(5) Å, respectively). In complex **12c**, the Mn is bound to five carbons of the central six-membered ring, shifted slightly away from the substituents on the ring as shown by the shorter Mn-to-C8 and -C9 distances (2.118(3), 2.138(3) Å, respectively) when compared with those of Mn to C4, C5, and C7 (2.292(3), 2.187(3), 2.212(3) Å, respectively). Crystallographic data were collected using a Syntex $P2_1$ diffractometer with Mo Kα radiation ($\lambda = 0.710\,73$ Å). The SHELXTL PLUS program set was used in refinement (Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990). Complex **7**: orthorhombic $P2_12_12_1$, $a = 7.651(2)$ Å, $b = 13.163(3)$ Å, $c = 18.174(4)$ Å, $V = 1830.4(8)$ Å^3, $Z = 4$. The intensity data were collected from $3.5 \leq 2\theta \leq 50°$ at 133 K. All hydrogens were located from difference Fourier maps and refined with use of a riding model. Refinement to convergence of the 240 parameters on 2673 unique data with $|F_o| > 6.0\sigma(|F_o|)$ gave $R = 3.99\%$, $R_w = 4.79\%$, GOF = 1.20. (Refinement of the enantiomeric configuration converged to $R = 6.17\%$, $R_w = 6.45\%$, and GOF = 1.52.) All unique data (3242 reflections) gave $R = 5.05\%$, $R_w = 5.10\%$. Complex **12c**: monoclinic $C2$, $a = 19.565(4)$ Å, $b = 6.9440(10)$ Å, $c = 14.228(3)$ Å, $\beta = 97.67(3)°$, $V = 1915.7(6)$ Å^3, $Z = 4$. The intensity data were collected from $3.5 \leq 2\theta \leq 50°$ at 294 K. Phenyl hydrogens were placed in ideal positions. All other hydrogens were located from difference Fourier maps and refined with use of a riding model. Refinement to convergence of the 252 parameters on 2057 unique data with $|F_o| > 2.0\sigma(|F_o|)$ gave $R = 2.64\%$, $R_w = 3.91\%$, and GOF = 1.02; all unique data (2127 reflections) gave $R = 2.74\%$, $R_w = 3.94\%$.

(10) For an earlier example of X-ray crystal structure determination of a cationic hexamethylbenzene–$Mn(CO)_3$ complex, see: Van Rooyen, P. H.; Geer, L.; Lotz, S. *Acta Crystallogr.* **1990**, *C46*, 1432. A (neutral) sulfur-containing arene–manganese complex has also recently been characterized by X-ray diffraction: Schindehutte, M.; van Rooyen, P. H.; Lotz, S. *Organometallics* **1990**, *9*, 293.